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GENETIC POLYMORPHISM OF MATRIX METALLOPROTEINASE 9 AND SUSCEPTIBILITY TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A META-ANALYSIS

GENETSKI POLIMORFIZAM MATRIKS METALOPROTEINAZE 9 I OSETLJIVOST NA OPSTRUKTIVNU BOLEST PLUĆA: META ANALIZA

Xiaoping Yang^{1#}, Yuanyuan Yu^{2#}, Yong Wang1, Wen Jiang¹, Wenqing Jiang¹, Bin Yin^{1*}

¹Department 2 of Respiratory and Critical Care (Lung disease) Center, Qingdao Hospital of Traditional Chinese Medicine (Haici Hospital), Qingdao, China ²Department of Anesthesiology, Qingdao Hospital of Traditional Chinese Medicine (Haici Hospital), Qingdao, China

Summary

Background: To systematically analyze the influence of genetic polymorphisms of matrix metalloproteinase 9 (MMP9) on susceptibility to chronic obstructive pulmonary disease (COPD).

Methods: Relevant literatures reporting MMP9 and susceptibility to COPD in PubMed, Web of Science, VIP, Wanfang and CNKI databases were searched using the key words »matrix metalloproteinases 9/MMP9, COPD/chronic obstructive pulmonary disease«. Data of eligible literatures were extracted and analyzed for the odds ratio (OR) and corresponding 95% CI.

Results: A total of 16 independent studies reporting MMP9-1562C/T and COPD patients were enrolled and analyzed. None of the genetic models revealed the relationship between MMP9-1562C/T and susceptibility to COPD. Subgroup analyses identified lower risk of COPD in Chinese population carrying the TT genotype for theMMP-9 rs3918242 relative to those carrying CT and CC genotypes (P=0.03, OR=0.67, 95% CI=0.46–0.97).

Conclusions: Chinese population carrying the TT genotype for the MMP-9 rs3918242 present lower susceptibility to COPD relative to those carrying CT and CC genotypes.

Keywords: MMP9, polymorphism, COPD, meta-analysis

Kratak sadržaj

Uvod: Sistematska analiza uticaja genetskih polimorfizama matriks metaloproteinaze 9 (MMP9) na osetljivost hronične opstruktivne bolesti pluća (HOBP).

Metode: Relevantna literatura koja izveštava o MMP9 i podložnosti HOBP u bazama podataka PubMed, Web of Scince, VIP, Wanfang i CNKI pretraživana je korišćenjem ključnih reči »matriks metaloproteinaze 9/MMP9, COPD/hronična opstruktivna bolest pluća«. Podaci iz kvalifikovane literature su ekstrahovani i analizirani za odnos šanse (OR) i odgovarajući 95% CI.

Rezultati: Ukupno je uključeno i analizirano 16 nezavisnih studija koje su izveštavale o pacijentima sa MMP9-1562C/T i HOBP. Nijedan od genetskih modela nije otkrio vezu između MMP9-1562C/T i osetljivosti na HOBP. Analize podgrupa identifikovale su niži rizik od HOBP kod kineske populacije koja nosi TT genotip za MMP-9 rs3918242 u odnosu na one koji nose CT i CC genotipove (P=0,03, OR=0,67, 95% CI=0,46–0,97).

Zaključak: Kineska populacija koja nosi TT genotip za MMP-9 rs3918242 predstavlja manju osetljivost na HOBP u odnosu na one sa CT i CC genotipovima.

Ključne reči: MMP9, polimorfizam, HOBP, meta-analiza

Address for correspondence:

Tel: 860532-83776223

e-mail: qd0532yb@163.com

Bin Yin, MM. Department 2 of Respiratory and Critical Care (Lung disease) Center, Qingdao Hospital of Traditional Chinese Medicine (Haici Hospital), 4 Renmin Road, Shibei District, Qingdao, Shandong 266033, China

[#] Xiaoping Yang and Yuanyuan Yu contributed equally to this work

Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide disease affecting approximately 3 million people. It is estimated that COPD will be the third leading cause of death by 2020 (1). As a chronic airway inflammatory disease, COPD is characterized by incomplete reversible airflow limitation, inflammatory cell infiltration, excessive mucus secretion, and airway remodeling (2). The precise molecular mechanism underlying the pathogenesis of COPD remains unclear. At present, it is generally believed that several risk factors are directly related to the pathogenesis of COPD, including host and environmental factors (3). Among environmental factors, smoking, exposure to chemicals, indoor and outdoor air pollution are risk factors for COPD (4). Host factors of COPD include antitrypsin-1, excessive deposition of extracellular matrix (ECM), corticosteroids, inflammatory stimuli, and metabolic imbalances (5, 6).

Matrix metalloproteinases (MMPs) are members of the metformin group and they are capable of degrading ECMs and regulating extracellular signaling networks (7). MMPs are important in COPD. They degrade matrix proteins (elastin, collagen) during the disease progression (8). In the past decade, abundant researches have been conducted to analyze the relationship between single nucleotide polymorphisms (SNPs) of MMPs and COPD risk in some populations (9–12). However, the conclusions were controversial. Some reports demonstrated the certain influence of MMPs on the occurrence of COPD (13-18), while others did not (9, 12, 19, 20). These conflicting findings may be explained by limited sample size, false positive results, and publication bias. In this paper, we performed a comprehensive meta-analysis to assess the influence of MMP polymorphisms on COPD.

Materials and Methods

Search strategy of literatures

Relevant literatures reporting the relationship between polymorphisms of MMP9-1562C/T and susceptibility to COPD in PubMed, Web of Science, VIP, Wanfang and CNKI databases were searched using the key words »matrix metalloproteinases 9/MMP9, COPD/chronic obstructive pulmonary disease«. There were no limitations on published languages. Citations in each literature were manually reviewed.

Inclusive and exclusive criteria

Inclusive criteria were as follows:1) Case-control studies conducted in humans; 2) Literatures published complete data or raw data that could calculate the genotype distribution; 3) COPD patients underwent diagnosis of pulmonary function index; 4) Literatures were conducted on the influence of polymorphisms of MMP9-1562C/T on susceptibility to COPD.

Exclusive criteria were as follows: 1) Repeated literatures; 2) Literatures lacked valid raw data; 3) Reviews, comments, animal experiments, researches on mechanism and case reports;4) The latest studies or those with a larger sample size were selected if data overlapping; 5) Unpublished data.

Flow diagram of literature searching was depicted in *Figure 1*.

Data extraction

Data were independently extracted and analyzed by two researchers, and the third one was responsible for solving any disagreement. Extracted data included: 1) Baseline data of literatures, including publication origin, first author, year or publication, and etc.; 2) Basic characteristics of subjects, including sample size, research country, genotype number and distribution, HWE in control group and etc.

Statistical analysis

Heterogeneity test was conducted by calculating odds ratio (OR) and the corresponding 95% CI with the I^2 test and the Q test. The pooled OR in studies lacking the heterogeneity was calculated by the fixeffects model. Otherwise, a random-effects model was used. Sensitivity analysis was performed by removing one study each time and analyzing the remaining in a combination way. The HWE of control genotype distribution was evaluated using the χ^2 test and P<0.05 considered as inequivalent. Publication bias was evaluated by depicting funnel plots and quantified by Egger's test. Data analyses were carried out using RevMan 5.3 and STATA12.0.

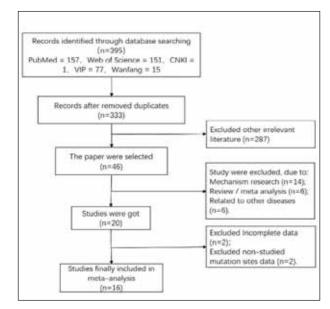


Figure 1 Flow diagram of the publication selection process.

Results

Baseline characteristics of eligible literatures

Initially, 157 literatures in PubMed, 151 in Web of Science, 1 in CNKI, 77 in VIP and 15 in Wanfang database were searched out, with a total of 395 literatures. A total of 62 replicates and 287 irrelevant

literatures were excluded after the first-round screening. Subsequently, 14 literatures on mechanisms, 6 reviews, 6 literatures reporting other diseases, 2 literatures without complete data and 2 reporting other mutant sites were excluded. Finally, 16 literatures were included in this study (*Figure 1*).

Table	Main	characteristics	of	studies	included	in	the	meta-analysis.
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Author	Year	Country	Journal name/ publication origin	Genotyping methods	SNP loci (P _{HWE})	Sample size	Control	Sample
Zhou	2004	China	Chinese Medical Journal	PCR- sequence	rs3918242 (p _{HWE} =0.92)	100 (male=98, female=)	100 (male=99, female=1)	Whole blood
lsao Ito	2005	Japan	Am J Respir Crit Care Med	PCR-RFLP	rs3918242 (p _{HWE} =0.41)	84 (male=81, female=3)	85 (male=69, female=16)	
Zhang Rongbao	2005	China	Chin J Epidemiol	PCR-RFLP	rs3918242 (p _{HWE} =0.09)	147 (male=135, female=12)	120 (male=110, female=10)	Whole blood
Han	2006	Asian	Chin J Tuberc Respir Dis	PCR-RFLP	rs3918242 (p _{HWE} =0.48)	60	52	Whole blood
Testaigzi	2006	Caucasian	Int J Chron Obstruct Pulmon Dis	PCR-RFLP	rs3918242 (p _{HWE} =0.39)	123	262	Whole blood
Korytina	2008	Russia	Russian Journal of Genetics	PCR-RFLP	rs3918242 (p _{HWE} =0.53)	318	319	Whole blood
Shih-Lung Cheng	2009	Taiwan (China)	Biochem Genet	PCR-RFLP	rs3918242 (p _{HWE} =0.23)	184 (male=152, female=32)	212 (male=182, female=30)	Whole blood
H. Schirmer	2009	Brazil	Genetics and Molecular Research	PCR	rs3918242 (p _{HWE} =0.60)	89	97	Whole blood
Shih-Yup Lee	2010	Korean	Basic Science Investigations	PCR-sequence	rs3918242 (p _{HWE} =0.376)	301	333	Whole blood
Hua	2010	China	Int J Respi	PCR-RFLP	rs3918242 (p _{HWE} =0.04)	180 (male=142, female=38)	180 (male=130, female=50)	Whole blood
Korytina	2012	Russia	Molecular Biology	PCR-RFLP	rs3918242 (p _{HWE} =0.67)	391	514	Whole blood
Sarra Bchir	2015	Tunisia	Mol Diagn Ther	PCR-RFLP	rs3918242 (p _{HWE} =0.02)	138 (male=122, female=16)	216 (male=155, female=61)	Whole blood
Marja Stankovic	2016	Serbia	Environmental and Molecular Mutagenesis. PCR-RFLP	rs3918242 (pHWE=0.28)	86	100		Whole blood
Marja Stankovic	2017	Serbia	JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE	PCR-RFLP	rs3918242 (p _{HWE} =0.28)	122	100	Whole blood
Tan Jie	2017	China	Journal Of Inner Mongolia Medical Universit	PCR-RFLP	rs3918242 (p _{HWE} <0.001)	186 (male=92, female=294)	219 (male=105, female=112)	Whole blood
Lwona Gilowska	2018	Poland	BioMed Research International	PCR-RFLP	rs3918242 (p _{HWE} =0.33)	335 (male=87, female=248)	309 (male=229, female=80)	Whole blood

SNP=Single nucleotide polymorphism; HWE = Hardy-Weinberg equilibrium; pHWE=p-value of Hardy-Weinberg Equilibrium test in controls for each locus; PCR = polymerase chain reaction

Baseline characteristics of eligible literatures were listed in *Table I*. Briefly, 16 case-control studies were published from 2004–2018, including 13 studies published in English-language scientific journals and 3 in Chinese-language scientific journals. Genotyping methods were conducted using polymerase chain reaction (PCR), PCR-RFLP and PCR-sequence. Identification of single nucleotide polymorphisms (SNPs) was conducted by extracting blood samples of subjects.

In the 16 eligible literatures, 5 analyzed Chinese population, 1 analyzed Japanese population, 2 analyzed Russian population, 1 analyzed Brazilian population, 1 analyzed Korean population, 1 analyzed Tunisian population, 2 analyzed Serbian population, 1 analyzed Poland population, 1 analyzed Asian population and 1 analyzed Caucasian population. Sample size of each literature was 60-391.

Meta-analysis

A total of 2011 COPD patients and 2249 healthy controls were enrolled. The influence of MMP9 (-1562) C/T on susceptibility to COPD was assessed using different genetic models. No relationship was found between the CC vs.TT genotype of MMP9 rs391842 and susceptibility to COPD in the allele model (P=0.41, OR=1.12, 95% CI=0.86-1.47) (*Figure 2 A-C*). The other three genetic models obtained the same conclusion, including the dominant model (CC vs. CT+TT, P=0.13, OR=0.82, 95% CI=0.63-1.06), recessive model (TT vs. CC+CT, P=0.87, OR=0.97, 95% CI=0.65-1.43) and over-dominant model (CT vs. CC+TT, P=0.51, OR=1.13, 95% CI=0.79-1.61).

Subgroup analyses were performed based on the ethnic populations, involving Asian population (8 literatures), European population (3 literatures), Caucasian population (3 literatures) and African population (2 literatures). The random-effects model was utilized owing to the different degrees of hetero-

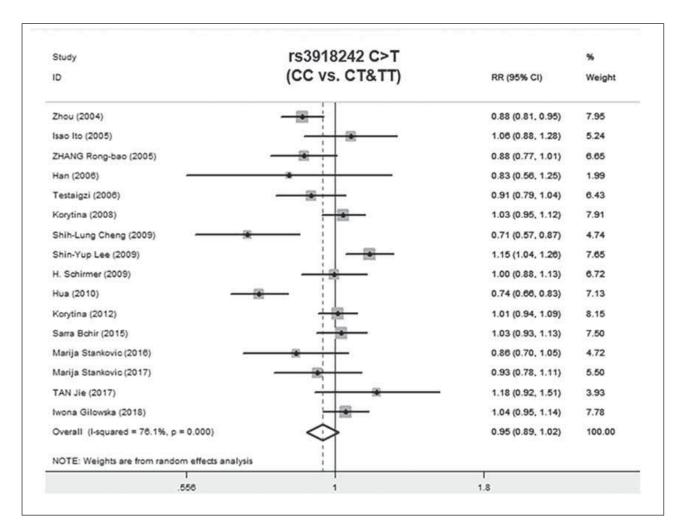


Figure 2A Forest map of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD.

Sarra Bchir (2015)

TAN Jie (2017)

Marija Stankovic (2016)

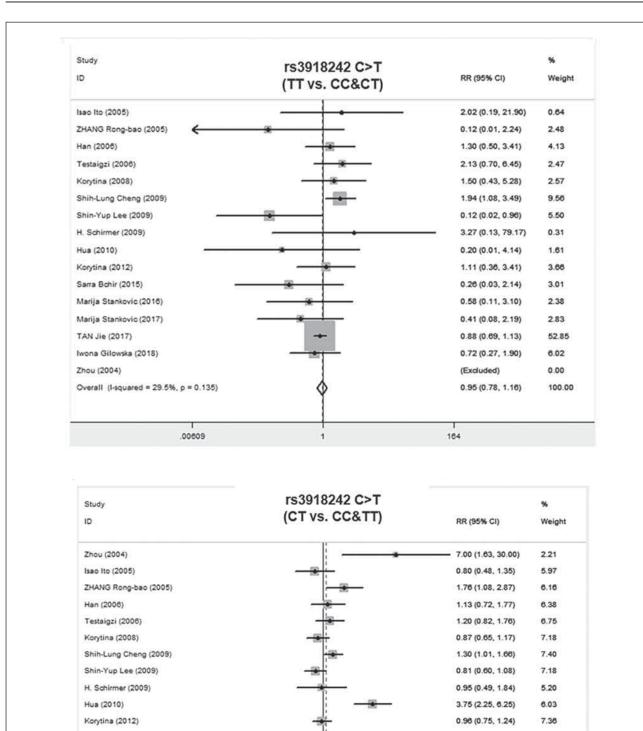
Marija Stankovic (2017)

Iwona Gilowska (2018)

Overall (I-squared = 84.6%, p = 0.000)

NOTE: Weights are from random effects analysis

0333



1.00 (0.62, 1.61)

1.50 (0.96, 2.35)

1.30 (0.84, 2.01)

0.16 (0.09, 0.27)

0.91 (0.68, 1.21)

1.08 (0.84, 1.40)

30

6.22

6.38

6.45

5.89

7.24

100.00

Figure 2B Forest map of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD.

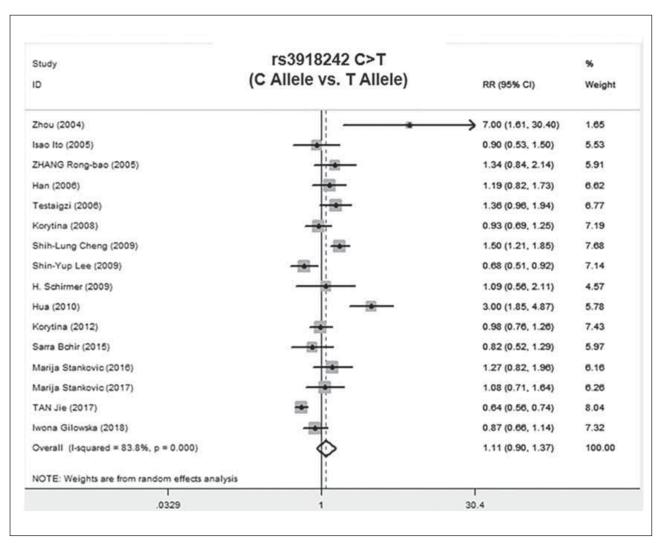


Figure 2C Forest map of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD.

geneity (I^2 >50%, P<0.05). The data showed no relationship between MMP9 polymorphisms and COPD risk under the different genetic models (P>0.05) (*Figure 3 C-D*).

Subsequently, we individually analyzed the relationship between MMP9 polymorphisms and COPD in Chinese population, involving 5 literatures (15, 18, 21–23). Except for the recessive model (TT vs. CC&CT) analyzed by the fix-effects model (P=0.13, I^2 =46%), the remaining were assessed using the random-effects model ($I^{\bar{2}}$ >50%, P<0.05) (Figure 4). Our data showed that Chinese population carrying the TT genotype for the MMP-9 rs3918242 was closely related to susceptibility to COPD relative to those carrying CT and CC genotypes (P=0.03, OR=0.67, 95% CI=0.46-0.97). Such a difference was not observed in the dominant model (CC vs. CT&TT), over-dominant model (CT vs. CC&TT) and allele model (C Allele vs. T Allele) (P>0.05) (Figure 4).

Heterogeneity and sensitivity analysis

Significant heterogeneity was identified in the dominant model, over-dominant model and allele model analyzing the relationship between MMP9 (-1562) C/T and susceptibility to COPD (all P<0.001). No remarkable changes in I^2 and P values were observed after removing a single study. In addition, sensitivity analysis was not altered by removing any study each time (data not shown).

In the subgroup analyses based on different ethnic populations, all genetic models showed the results of $I^2 > 50\%$ and P < 0.05. We did not find any changes in I^2 and P values after removing a single study. Sensitivity analysis was not influenced by removing a single study (data not shown).

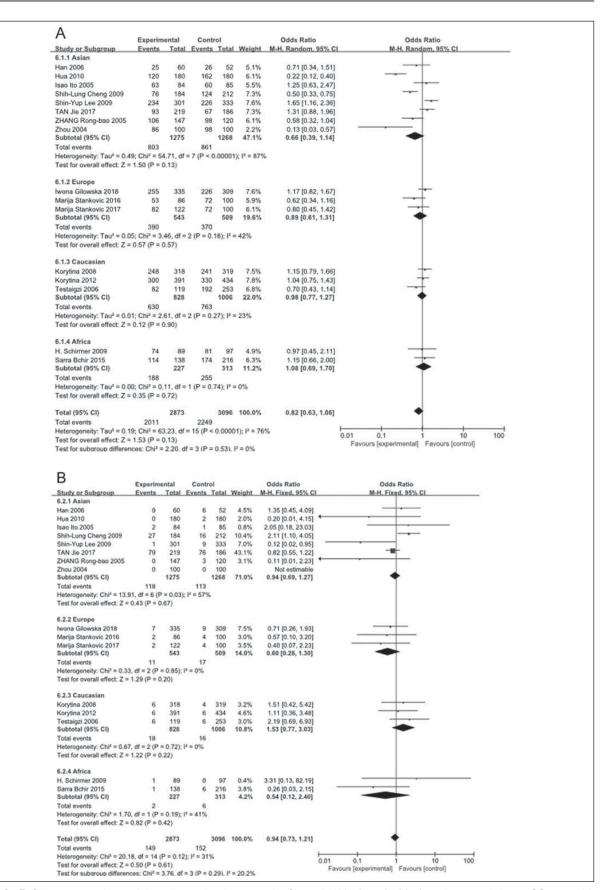


Figure 3A, B Subgroup analyses of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD in different regions and different pairs of comparisons.

-	Experim	Intal	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Experime				Weight	Odds Ratio M-H. Random, 95% C	
6.3.1 Asian	Events	Total	Events	Total	weight	M-H, Kandom, 957a C	M-H, Random, 95% CI
Han 2006	26	60	20	52	5.7%	1.22 [0.57, 2.61]	
Hua 2010	60	180	16	180	6.3%	5.13 [2.81, 9.33]	
Isao Ito 2005	19	84	24	85	5.9%	0.74 [0.37, 1.49]	
Shih-Lung Cheng 2009	81	184	72	212	7.0%	1.53 [1.02, 2.30]	
Shin-Yup Lee 2009	59	301	81	333	7.1%	0.76 [0.52, 1.11]	
TAN Jie 2017	14	219	76	186	6.2%	0.10 [0.05, 0.18]	
ZHANG Rong-bao 2005	41	147	19	120	6.3%	2.06 [1.12, 3.78]	
Zhou 2004	14	100	2	100	3.2%	7.98 [1.76, 36.10]	
Subtotal (95% CI)		1275	240	1268	47.6%	1.23 [0.55, 2.73]	
Total events Heterogeneity: Tau ² = 1.1 Test for overall effect: Z =			310 = 7 (P <	0.0000	1); l² = 93	%	
6.3.2 Europe							
Iwona Gilowska 2018	73	335	74	309	7.1%	0.88 [0.61, 1.28]	
Marija Stankovic 2016	31	86	24	100	6.2%	1.78 [0.95, 3.37]	
Marija Stankovic 2017	38	122	24	100	6.3%	1.43 [0.79, 2.60]	
Subtotal (95% CI)	157	543		509	19.5%	1.23 [0.79, 1.92]	*
Total events Heterogeneity: Tau ² = 0.0	142 8: Chill = 4 3	29 df = 1	122 2 (P = 0 1	12): l² =	53%		
Test for overall effect: Z =			c (r = 0.	(6),1 -	0070		
6.3.3 Caucasian	22.02	121000		I group			
Korytina 2008	64	318	74	319	7.1%	0.83 [0.57, 1.22]	T
Korytina 2012	85	391	98	434	7.2%	0.95 [0.69, 1.32]	—
Testaigzi 2006 Subtotal (95% CI)	31	119 828	55	253 1006	6.6% 20.9%	1.27 [0.76, 2.11] 0.96 [0.77, 1.20]	•
Total events	180	010	227	1000	20.37	0.00 [0.77, 1.20]	T
Total events Heterogeneity: Tau ² = 0.0		9 AF = 1		135-12-	0%		
Test for overall effect: Z =			e (r- = 0,4	-3), F =	578		
		1000					
6.3.4 Africa							
H. Schirmer 2009	14	89	16	97	5.6%	0.94 [0.43, 2.07]	
Sarra Bchir 2015	23	138	36	216	6.4%	1.00 [0.56, 1.77]	
Subtotal (95% CI)	(22)	227	227	313	12.0%	0.98 [0.62, 1.56]	T
Total events	37		52				
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =			1 (P = 0.5	91); I* =	070		
Total (95% CI)		2873		3096	100.0%	1.13 [0.79, 1.61]	•
Heterogeneity: Tau ^z = 0.4 Test for overall effect: Z =	0.66 (P = 0	.51)				6%	0.01 0.1 1 10 100 Favours (experimental] Favours (control)
Heterogeneity: Tau ² = 0.4 Test for overall effect: Z = Test for subaroup differen	3; Chi ² = 10 0.66 (P = 0	.51)	= 15 (P -			5%	
Heterogeneity: Tau ² = 0.4: Test for overall effect: Z = Test for subaroup differen	3; Chi ² = 10 0.66 (P = 0 ces: Chi ² = Experime	.51) 1.21. df	= 15 (P + = 3 (P =	0.75). I	¹² = 0%	Odds Ratio	Favours (experimental) Favours (control) Odds Ratio
Heterogeneity: Tau ² = 0.4; Test for overall effect: Z = Test for subaroup differen D Study or Subgroup	3; Chi ² = 10 0.66 (P = 0 ces: Chi ² =	.51) 1.21. df	= 15 (P + = 3 (P =	0.75). I	¹² = 0%		Favours (experimental) Favours (control)
Heterogeneity: Tau ⁴ = 0.4: Test for overall effect: Z = Test for subaroup differen D Study or Subgroup 6.4.1 Asian	3: Chi ² = 10 0.66 (P = 0 cces: Chi ² = Experime Events	51) 1.21. df ental Total	= 15 (P + = 3 (P = Contro <u>Events</u>	0.75). ol <u>Total</u>	¹² = 0% Weight	Odds Ratio M-H. Random, 95% Cl	Favours (experimental) Favours (control) Odds Ratio
Hetsrogeneity: Tau ⁴ = 0.4; Test for overall effect: Z = Test for subgroup differen D Study or Subgroup 6.4.1 Asian Shih-Lung Cheng 2009	3: Chi ² = 10 0.66 (P = 0 ces: Chi ² = Experime Events 44	2.51) 1.21. df ental <u>Total</u> 120	= 15 (P + = 3 (P = Contro Events 32	0.75). I ol <u>Total</u> 104	¹² = 0% <u>Weight</u> 6.8%	Odds Ratio M-H. Random, 95% Cl 1.30 [0.75, 2.28]	Favours (experimental) Favours (control) Odds Ratio
Heterogeneity: Tau ² = 0.4: Test for overall effect: Z = Test for subaroup differen D Study or Subgroup 6.4.1 Asian	3: Chi ² = 10 0.66 (P = 0 cces: Chi ² = Experime Events	51) 1.21. df ental Total	= 15 (P + = 3 (P = Contro <u>Events</u>	0.75). ol <u>Total</u>	¹² = 0% Weight	Odds Ratio M-H. Random, 95% Cl	Favours (experimental) Favours (control) Odds Ratio
Heterogeneity: Tau ² = 0.4: Test for overall effect: Z = Test for subaroup differen D Study or Subgroup 6.4.1 Asian Shih-Lung Cheng 2009 Shin-Yup Lee 2009	3; Chi ² = 10 0.66 (P = 0 ces: Chi ² = Experime Events 44 60	2.51) 1.21. df ental <u>Total</u> 120 360	= 15 (P + = 3 (P = Contro Events 32 20	0.75). I ol <u>Total</u> 104 360	² = 0% <u>Weight</u> 6.8% 7.0%	Odds Ratio M-H. Random, 95% CI 1.30 [0.75, 2.28] 3.40 [2.00, 5.77]	Favours (experimental) Favours (control) Odds Ratio
Heterogeneity: Tau ² = 0.4: Test for overall effect: Z = Test for subaroup differen D Study or Subgroup 6.4.1 Asian Shih-Lung Cheng 2009 Shin-Yup Lee 2009 TAN Jia 2017 ZHANG Rong-bao 2005 Zhou 2004	3: Chi ² = 10 0.66 (P = 0 ces: Chi ² = Experime Events 44 60 23	1.21. df 1.21. df ntal <u>Total</u> 120 360 168 368 602	= 15 (P = = 3 (P = Contro Events 32 20 26 104 99	0.75). I Total 104 360 170 424 666	² = 0% Weight 6.8% 7.0% 6.3% 9.3% 9.0%	Odds Ratio M.H. Random, 95% CI 1.30 [0.75, 2.28] 3.40 [2.00, 5.77] 0.88 [0.48, 1.61] 1.76 [1.31, 2.42] 0.65 [0.46, 0.91]	Favours (experimental) Favours (control) Odds Ratio
Hetsrogeneity: Tau ² = 0.4; Test for overall effect: Z = Test for subaroup differen <u>Study or Subgroup</u> 6.4.1 Asian Shih-Lung Cheng 2009 Shin-Yup Lee 2009 TAN Jia 2017 ZHANG Rong-bao 2005 Zhou 2004 Subtotal (95% CI)	3; Chi ² = 10 0.66 (P = 0 cces: Chi ² = Experime Events 44 60 23 135 61	1.21. df 1.21. df ental <u>Total</u> 120 360 168 368	= 15 (P = = 3 (P = <u>Events</u> 32 20 26 104 99	0.75). I bl Total 104 360 170 424	¹² = 0% <u>Weight</u> 6.8% 7.0% 6.3% 9.3%	Odds Ratio M.H. Random, 95% CI 1.30 [0.75, 2.28] 3.40 [2.00, 5.77] 0.88 [0.48, 1.61] 1.76 [1.31, 2.42]	Favours (experimental) Favours (control) Odds Ratio
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Heterogeneity: Tau ⁴ = 0.4: Test for overall effect: Z = Test for subaroup differen D. Study or Subgroup 6.4.1 Asian Shih-Lung Cheng 2009 Shin-Yup Lee 2009 TAN Jie 2017 ZHANG Rong-bao 2005 Zhou 2004 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.3	3; Chi ² = 10 0.66 (P = 0 ces: Chi ² = Experime Events 44 60 23 135 61 323 8; Chi ² = 34	.51) 1.21. df 1.21. df 120 360 168 368 368 602 1618 .62, df =	= 15 (P = = 3 (P = Contro Events 32 20 26 104 99 281	0.75). I Total 104 360 170 424 666 1724	² = 0% <u>Weight</u> 6.8% 7.0% 6.3% 9.3% 9.0% 38.3%	Odds Ratio M.H. Random, 95% CI 1.30 [0.75, 2.28] 3.40 [2.00, 5.77] 0.88 [0.48, 1.61] 1.76 [1.31, 2.42] 0.65 [0.46, 0.91]	Favours (experimental) Favours (control) Odds Ratio
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Heterogeneity: Tau ² = 0.4; Test for overall effect: Z = Test for subaroup differen Study or Subaroup 6.4.1 Asian Shih-Lung Cheng 2009 Shin-Yup Lee 2009 TAN Jie 2017 ZHANG Rong-bao 2005 Zhou 2004 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = 6.4.2 Europe Iwona Gilowska 2018 Marija Stankovic 2017 Marija Stankovic 2017 Total events Heterogeneity: Tau ² = 0.0 Total events Heterogeneity: Tau ² = 0.0 Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 6.4.3 Caucasian Korytina 2012 Testagizi 2006 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 6.4.4 Africa H. Schirmer 2009 Sarra Bchir 2015 Subtotal (95% CI) Total events	3: Chi ² = 10 0.66 (P = 0 cces: Chi ² = Experime 44 60 23 135 61 323 135 61 323 135 145 100 (P = 0 23 87 35 145 100 (P = 0 76 97 43 216 125 161 25 41 100 (Ch ² = 3,(0.43 (P = 0 16 25 41 100 (Ch ² = 0,(0.57 (P = 0 725)	(51) 1.21. df 1.21. df 1.21. df 1.21. df 1.20. 360 1638 602 1618 602 1618 670 172 1010 14. df = 2 238 1656 676 177 1010 14. df = 2 238 1656 178 276 454 454 454 4738	= 15 (P + = 3 (P = Contrr Events 32 20 20 104 99 281 4 (P < 0, 281 4 (P < 0, 281 281 4 (P < 0, 281 281 4 (P < 0, 281 281 4 (P < 0, 281 4 (P <	0.75). 1 Total 104 360 170 424 666 1724 00001) 170 618 808 506 2012 2); I ² = 194 432 626 8); I ² = 5350	² = 0% Weight 6.8% 7.0% 6.3% 9.0% 38.3% 9.0% 38.3% 9.2% 7.2% 22.5% 6% 9.4% 8.1% 26.6% 35% 5.3% 7.2% 12.6% 0% 100.0%	Odds Ratio M-H. Random, 95% Cl 1.30 [0.75, 2.28] 3.40 [2.00, 5.77] 0.88 [0.48, 1.61] 1.78 [1.31, 2.42] 0.65 [0.46, 0.91] 1.34 [0.75, 2.40] 0.88 [0.48, 1.61] 0.85 [0.62, 1.17] 1.34 [0.79, 2.28] 0.95 [0.73, 1.24] 0.95 [0.73, 1.24] 0.95 [0.73, 1.31] 1.44 [0.95, 2.20] 1.06 [0.83, 1.35] 1.10 [0.53, 2.27] 0.80 [0.48, 1.33] 0.89 [0.58, 1.34] 1.12 [0.89, 1.42]	Favours (experimental) Favours (control) Odds Ratio
Heterogeneity: Tau ² = 0.4; Test for overall effect: Z = Test for subaroup differen 0 <u>Study or Subaroup</u> 6.4.1 Asian Shih-Lung Cheng 2009 Shin-Yup Lee 2009 TAN Jie 2017 ZHANG Rong-bao 2005 Zhou 2004 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = 6.4.2 Europe Iwona Gilowska 2018 Marija Stankovic 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 6.4.3 Caucasian Korytina 2008 Korytina 2012 Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 6.4.4 Africa H. Schirmer 2009 Sarra Bchir 2015 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 6.4.4 Africa H. Schirmer 2009 Sarra Bchir 2015 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	3; Chi ² = 10 0.66 (P = 0 cces: Chi ² = Experime 44 60 23 135 61 323 135 61 323 135 61 23 87 35 145 1.00 (P = 0 76 97 43 216 25 0. Chi ² = 34 1.00 (Chi ² = 34 1.00 (Chi ² = 34) 1.00 (Chi ² = 3.0) 0.43 (P = 0 1.00 (Chi ² = 3.0) 0.57 (P = 0 1.00 (Chi ² = 3.0) 1.00 (C	(51) 1.21. df 1.21. df 1.21. df 1.21. df 1.21. df 1.21. df 1.23. df	= 15 (P + = 3 (P = Contrr Events 32 20 20 104 99 281 4 (P < 0, 281 4 (P < 0, 281 281 4 (P < 0, 281 281 4 (P < 0, 281 281 4 (P < 0, 281 4 (P <	0.75). 1 Total 104 360 170 424 666 1724 00001) 170 618 808 506 2012 2); I ² = 194 432 626 8); I ² = 5350	² = 0% Weight 6.8% 7.0% 6.3% 9.0% 38.3% 9.0% 38.3% 9.2% 7.2% 22.5% 6% 9.4% 8.1% 26.6% 35% 5.3% 7.2% 12.6% 0% 100.0%	Odds Ratio M-H. Random, 95% CI 1.30 [0.75, 2.28] 3.40 [2.00, 5.77] 0.88 [0.48, 1.61] 1.78 [1.31, 2.42] 0.65 [0.46, 0.91] 1.34 [0.75, 2.40] 0.88 [0.48, 1.61] 0.85 [0.62, 1.17] 1.34 [0.79, 2.28] 0.95 [0.73, 1.24] 0.95 [0.73, 1.24] 0.92 [0.66, 1.28] 0.98 [0.73, 1.31] 1.44 [0.53, 2.27] 0.80 [0.48, 1.33] 0.89 [0.58, 1.34] 1.12 [0.89, 1.42]	Favours (experimental) Favours (control) Odds Ratio

Figure 3C, D Subgroup analyses of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD in different regions and different pairs of comparisons.

CC vs. CT&TT	Experim	ental	Contr	ol		Odds Ratio	Odd	s Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H. Ran	dom. 95% Cl
Hua 2010	120	180	162	180	21.1%	0.22 [0.12, 0.40]		011020020021
Shin-Yup Lee 2009	234	301	226	333	22.5%	1.65 [1.16, 2.36]		
TAN Jie 2017	93	219	67	186	22.3%	1.31 [0.88, 1.96]		+=-
ZHANG Rong-bao 2005	106	147	98	120	21.0%	0.58 [0.32, 1.04]		
Zhou 2004	86	100	98	100	13.1%	0.13 [0.03, 0.57]		
Total (95% CI)		947		919	100.0%	0.59 [0.26, 1.34]	-	-
Total events	639		651					
Heterogeneity: Tau ² = 0.75	5; Chi ² = 46	5.02, df =	4 (P < 0	.00001); 1² = 91%		0.01 0.1	1 10 1
Test for overall effect: Z =	1.26 (P = 0	0.21)					Favours [experimental]	1
TT vs. CC&CT	Experim	ental	Cont	rol		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Tota	Weight	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% Cl
Hua 2010	0	180	2	180	3.7%	0.20 [0.01, 4.15]	· · · · · · · · · · · · · · · · · · ·	Contraction of the second s
Shin-Yup Lee 2009	1	301	9	333	12.6%	0.12 [0.02, 0.95]		
TAN Jie 2017	79	219	76	1.000	6 MARKEN	0.82 [0.55, 1.22]	-	-
ZHANG Rong-bao 2005	0	147	3	120	5.7%	0.11 [0.01, 2.23]	• •	
Zhou 2004	0	100	0	100		Not estimable		
Total (95% CI)		947		919	100.0%	0.67 [0.46, 0.97]	•	ç.
Total events	80		90					
Heterogeneity: Chi ^z = 5.59), df = 3 (P	= 0.13)	l ² = 46%			•	1	1
Test for overall effect: Z =						30	0.01 0.1 Favours [experimental]	1 10 10 Favours (control)
CT vs. CC&TT	Experim	Intal	Contr	ol		Odds Ratio		s Ratio
Study or Subgroup	Events				Wolcht	M-H, Random, 95% CI		dom. 95% Cl
Hua 2010	60	180	16	180	20.6%	A PARTY AND A CONTRACTOR OF A PARTY AND A	men, cau	
	59	301	81	333	21.2%	5.13 [2.81, 9.33]		-
Shin-Yup Lee 2009 TAN Jie 2017	14	219	76	186	20.6%	0.76 [0.52, 1.11] 0.10 [0.05, 0.18]		
ZHANG Rong-bao 2005	41	147	19	120	20.6%	2.06 [1.12, 3.78]		
Zhou 2004	14	100	2	100	17.0%	7.98 (1.76, 36.10)		
Total (95% CI)		947		919	100.0%	1.35 [0.35, 5.25]		
Total events	188		194	8.08	1001010	tion faces, seed		
Heterogeneity: Tau ² = 2.2		155 df	10.55	00001	22 A 12 - 06%		H	1 1
Test for overall effect: Z =			40.00		1.1 - 5010		0.01 0.1 Favours [experimental]	1 10 10 Favours [control]
C Allele vs. T Allele Experim		perimental		Control		Odds Ratio	Odd	s Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	M-H. Ran	dom, 95% Cl
Hua 2010	60	360	20	360	21.1%	3.40 [2.00, 5.77]		
Shin-Yup Lee 2009	61	602	99	666	22.2%	0.65 [0.46, 0.91]	-	-
TAN Jie 2017	172	438	228	372	22.4%	0.41 [0.31, 0.54]		
ZHANG Rong-bao 2005	41	294	25	240	21.1%	1.39 [0.82, 2.37]		
Zhou 2004	14	200	2	200	13.3%	7.45 [1.67, 33.23]		
Total (95% CI)		1894		1838	100.0%	1.35 [0.58, 3.11]	-	•
	348		374					
Total events	h Chif = 64	1.50, df =	4 (P < 0	.00001); 1 ^z = 94%		0.01 0.1	1 10 10
Heterogeneity: Tau ^x = 0.86		49)					and the second sec	
),49)					Favours [experimental]	Favours [control]

Figure 4 Subgroup analyses of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD in Chinese population and different pairs of comparisons.

Publication bias

A wide range of search strategies was carried out to minimize potential publication biases. After quantification using Egger's test, the data showed no publication biases between MMP9 (-1562) C/T and

susceptibility to COPD in the three genetic models except for the allele model (CC vs. CT+TT, P=0.325; TT vs. CC+CT, P=0.541; CT vs. CC&TT, P=0.553; C allele vs. T allele, P=0.017) (*Figure 5*).

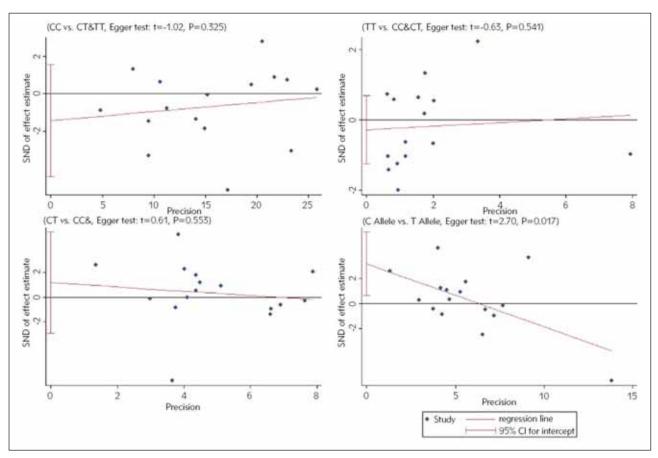


Figure 5 Subgroup analyses of the relationship between the SNP of MMP-9 rs3918242 and susceptibility to COPD in Chinese population and different pairs of comparisons.

Discussion

MMPs are a class of zinc-dependent endopeptidases that degrade major protein components of the ECM. They participate in development- and inflammation-related tissue remodeling and repair (7). MMP-9 (gelatinase B) can degrade ECM proteins, such as type IV collagen and gelatin (24). In addition, it exerts a vital role in airway inflammation and remodeling (25, 26). MMP-9 protects ventilatorinduced lung injury by reducing infiltration of alveolar neutrophils (27).

COPD is a common respiratory disease characterized by airflow limitation. The pathogenesis of COPD is complex, involving inflammatory response, oxidant-antioxidant imbalance, and MMPs-induced proteolysis of the alveolar wall. MMP9, one of the most widely studied MMPs, decomposes most of the components of ECM by degrading structural proteins, such as collagen and elastin (28). Many studies have reported the involvement of MMP9 in the development of lung diseases (29). MMP9 polymorphism is identified to increase the susceptibility to respiratory diseases (30–33). Multiple SNPs of MMP9 have been discovered. Among them, C/T mutation on MMP9 (-1562) rs3918242 results in the increased promoter activity owing to the deletion of the transcriptional repressor binding site (34).

So far, studies focusing on the correlation between MMP9 -1562 C/T polymorphism and COPD are relatively rare and uncertain. Studies with a small sample size lack the statistical power and often lead to contradictory conclusions. Meta-analysis provides convincing evidences by calculating data extracted from multiple studies. In this paper, we obtained the conclusion that MMP9 -1562 C/T polymorphism was not associated with susceptibility toped in different putative genetic models. Subgroup analyses showed that Chinese population carrying the TT genotype for the MMP-9 rs3918242 are risky of COPD relative to those carrying CT and CC genotypes.

Inconsistent with our results, some studies have demonstrated that the MMP9 -1562 C>T polymorphism indeed influences COPD risk. Zhou et al. (35) illustrated that the TT genotype of MMP9 -1562 C/T polymorphism is a genetic risk factor for severe COPD. Korytina et al. (36) have indicated the correlation between the TT genotype of MMP9 -1562 C/T polymorphism and COPD severity. Similarly, a study conducted in Russia showed a significant difference in the frequency distribution of MMP9 -1562 C>T among COPD patients with different severity levels (37).

Some shortcomings in this study should be pointed out. First of all, many complex factors were not adjusted, such as gender, age, and smoking history. Secondly, some studies (16, 20, 23) had small sample sizes and did not have enough capacity to detect the risk of COPD. Thirdly, the lack of raw data limited the further analysis of the potential interactions between genetic risks and environmental factors in COPD. Studies with large sample sizes in a multicenter hospital are required for further validation.

Conclusions

Chinese population carrying the TT genotype for the MMP-9 rs3918242 present lower susceptibili-

References

- Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ 2011; 342: d3215.
- Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet 2017; 389(10082): 1931–40.
- Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. Lancet 2011; 378(9795): 1015–26.
- Clancy J, Nobes M. Chronic obstructive pulmonary disease: nature-nurture interactions. Br J Nurs 2012; 21(13): 772–81.
- Yun CM, Sang XY. Role of proteinase-activated receptor-1 gene polymorphisms in susceptibility to chronic obstructive pulmonary disease. Genet Mol Res 2015; 14(4): 13215–20.
- Gan WQ, FitzGerald JM, Carlsten C, Sadatsafavi M, Brauer M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. Am J Respir Crit Care Med 2013; 187(7): 721–7.
- Churg A, Zhou S, Wright JL. Series »matrix metalloproteinases in lung health and disease«: Matrix metalloproteinases in COPD. Eur Respir J 2012; 39(1): 197–209.
- Ishii T, Abboud RT, Wallace AM, English JC, Coxson HO, Finley RJ, et al. Alveolar macrophage proteinase/antiproteinase expression in lung function and emphysema. Eur Respir J 2014; 43(1): 82–91.
- 9. Cheng SL, Yu CJ, Yang PC. Genetic polymorphisms of cytochrome p450 and matrix metalloproteinase in chronic obstructive pulmonary disease. Biochem Genet 2009; 47(7–8): 591–601.
- van Diemen CC, Postma DS, Aulchenko YS, Snijders PJ, Oostra BA, van Duijn CM, et al. Novel strategy to identify

ty to COPD relative to those carrying CT and CC genotypes.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

genetic risk factors for COPD severity: a genetic isolate. Eur Respir J 2010; 35(4): 768–75.

- Enewold L, Mechanic LE, Bowman ED, Platz EA, Alberg AJ. Association of matrix metalloproteinase-1 polymorphisms with risk of COPD and lung cancer and survival in lung cancer. Anticancer Res 2012; 32(9): 3917–22.
- Bchir S, Nasr HB, Hakim IR, Anes AB, Yacoub S, Garrouch A, et al. Matrix Metalloproteinase-9 (279R/Q) Polymorphism is Associated with Clinical Severity and Airflow Limitation in Tunisian Patients with Chronic Obstructive Pulmonary Disease. Mol Diagn Ther 2015; 19(6): 375–87.
- Mocchegiani E, Giacconi R, Costarelli L. Metalloproteases/anti-metalloproteases imbalance in chronic obstructive pulmonary disease: genetic factors and treatment implications. Curr Opin Pulm Med 2011; 17 Suppl 1: S11–9.
- Hernandez-Montoya J, Perez-Ramos J, Montano M, Ramirez-Venegas A, Sansores RH, Perez-Rubio G, et al. Genetic polymorphisms of matrix metalloproteinases and protein levels in chronic obstructive pulmonary disease in a Mexican population. Biomark Med 2015; 9(10): 979– 88.
- Lee SY, Kim MJ, Kang HG, Yoo SS, Choi YY, Lee WK, et al. Polymorphisms in matrix metalloproteinase-1, -9 and -12 genes and the risk of chronic obstructive pulmonary disease in a Korean population. Respiration 2010; 80(2): 133–8.
- Stankovic M, Kojic S, Djordjevic V, Tomovic A, Nagorni-Obradovic L, Petrovic-Stanojevic N, et al. Gene-environment interaction between the MMP9 C-1562T promoter variant and cigarette smoke in the pathogenesis of chronic obstructive pulmonary disease. Environ Mol Mutagen 2016; 57(6): 447–54.
- Tesfaigzi Y, Myers OB, Stidley CA, Schwalm K, Picchi M, Crowell RE, et al. Genotypes in matrix metalloproteinase

9 are a risk factor for COPD. Int J Chron Obstruct Pulmon Dis 2006; 1(3): 267–78.

- Zhou M, Huang SG, Wan HY, Li B, Deng WW, Li M. Genetic polymorphism in matrix metalloproteinase-9 and the susceptibility to chronic obstructive pulmonary disease in Han population of south China. Chin Med J (Engl) 2004; 117(10): 1481–4.
- Haq I, Chappell S, Johnson SR, Lotya J, Daly L, Morgan K, et al. Association of MMP-2 polymorphisms with severe and very severe COPD: a case control study of MMPs-1, 9 and 12 in a European population. Bmc Med Genet 2010; 11: 7.
- Ito I, Nagai S, Handa T, Muro S, Hirai T, Tsukino M, et al. Matrix metalloproteinase-9 promoter polymorphism associated with upper lung dominant emphysema. Am J Respir Crit Care Med 2005; 172(11): 1378–82.
- Hua DM, Ding LY, Wang Z, Lv FZ, Xiao JL, Chi P, Zhuo JM. Study on Genetic Polymorphism of Matrix Metalloproteinase 9 and Susceptibility to Chronic Obstructive Pulmonary Disease in Tibet. Int J Respi 2010; 30: 1157– 60.
- Tan J, Bai YF, Sun C, Xu XX. Study on Genetic Polymorphism of MMP-9 and Susceptibility to COPD in Inner Mongolia. Journal of Inner Mongolia Medical University 2017; 39: 50–3, 59.
- Zhang RB, He QY, Yang RH, Lu BB, Liu YJ. Study on Genetic Polymorphism of Matrix Metalloproteinase 1, 9, 12 and Susceptibility to Chronic Obstructive Pulmonary Disease among Han Chinese in Northern China. Chin J Epidemiol 2005; 26: 907–10.
- 24. Newby AC. Dual role of matrix metalloproteinases (matrixins) in intimal thickening and atherosclerotic plaque rupture. Physiol Rev 2005; 85(1): 1–31.
- Kumar M, Phougat N, Ruhil S, Dhankhar S, Balhara M, Chhillar AK. Genomics of Chronic Obstructive Pulmonary Disease (COPD); Exploring the SNPs of Protease-Antiprotease Pathway. Curr Genomics 2013; 14(3): 204–13.
- Renckens R, Roelofs JJ, Florquin S, de Vos AF, Lijnen HR, Van'T VC, et al. Matrix metalloproteinase-9 deficiency impairs host defense against abdominal sepsis. J Immunol 2006; 176(6): 3735–41.
- Albaiceta GM, Gutierrez-Fernandez A, Parra D, Astudillo A, Garcia-Prieto E, Taboada F, et al. Lack of matrix metalloproteinase-9 worsens ventilator-induced lung injury. Am J Physiol Lung Cell Mol Physiol 2008; 294(3): L535– 43.
- Opdenakker G, Van den Steen PE, Dubois B, Nelissen I, Van Coillie E, Masure S, et al. Gelatinase B functions as

regulator and effector in leukocyte biology. J Leukoc Biol 2001; 69(6): 851–9.

- Öner Ö, Deveci F, Telo S, Kuluöztürk M, Balin M. MRproADM and MR-proANP levels in patients with acute pulmonary embolism J Med Biochem 2020; 39(3): 328–35.
- Xu L, Bian W, Gu XH, Shen C. Genetic polymorphism in matrix metalloproteinase-9 and transforming growth factor-beta1 and susceptibility to combined pulmonary fibrosis and emphysema in a Chinese population. Kaohsiung J Med Sci 2017; 33(3): 124–9.
- Liu JW, Chen DQ. Correlations of MMP-2 and MMP-9 gene polymorphisms with the risk of hepatopulmonary syndrome in cirrhotic patients: A case-control study. Kaohsiung J Med Sci 2018; 34(11): 634–42.
- Jiang S, Yang ZH, Chen YY, He Z, Zhou Y, Gao Y, et al. MMP-9 genetic polymorphism may confer susceptibility to COPD. Genet Mol Res 2016; 15(2): gmr.15026272.
- Zhang HT, Fang SC, Wang CY, Wang W, Wu J, Wang C, et al. MMP-9 1562C> T Gene Polymorphism and Efficacy of Glucocorticoid Therapy in Idiopathic Pulmonary Fibrosis Patients. Genet Test Mol Biomarkers 2015; 19(11): 591–7.
- Zhang B, Ye S, Herrmann SM, Eriksson P, de Maat M, Evans A, et al. Functional polymorphism in the regulatory region of gelatinase B gene in relation to severity of coronary atherosclerosis. Circulation 1999; 99(14): 1788– 94.
- 35. Zhou H, Wu Y, Jin Y, Zhou J, Zhang C, Che L, et al. Genetic polymorphism of matrix metalloproteinase family and chronic obstructive pulmonary disease susceptibility: a meta-analysis. Sci Rep 2013; 3: 2818.
- Korytina GF, Tselousova OS, Akhmadishina LZ, Victorova EV, Zagidullin S, Victorova TV. Association of the MMP3, MMP9, ADAM33 and TIMP3 genes polymorphic markers with development and progression of chronic obstructive pulmonary disease. Mol Biol (Mosk) 2012; 46(3): 487–99.
- Korytina GF, Akhmadishina LZ, Ianbaeva DG, Viktorova TV. Polymorphism in promoter regions of matrix metalloproteinases (MMP1, MMP9, and MMP12) in chronic obstructive pulmonary disease patients. Genetika 2008; 44(2): 242–9.

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